REMARKS/ARGUMENTS

Claims 1-4, 6-12, 14-15, and 17-40 are pending.

Claims 1, 9, 12, 17, and 18 have been amended.

Claims 29-40 have been added.

Support for the amendments is found in the claims and specification (e.g., page 1, lines 3-8; page 5, line 11 to page 6, line 24; page 7, lines 3-5; page 11, lines 6-11; page 11, lines 28-30; the Examples on pages 11-16 and page 15, lines 16 to page 16, line14; page 1, lines 15-30; page 3, lines 1-7; page 3, lines 14-16; page 4, lines 28-29), as originally filed. Claims 32-38 comprise the limitations of claims 10-12, 14-15, and 17-18.

No new matter is believed to have been added.

Applicants wish to thank the Examiner for a discussion on December 3, 2008. The indefiniteness, enablement and art rejections were discussed in view of the proposed amendments.

Claims 12 and 17-18 are rejected under 35 U.S.C. 112, second paragraph. The claims have been amended by introducing the limitations "the dendritic cells" and "a heterologous with the subject". It is believed that the claims are clear. Applicants request that the rejection be withdrawn.

Claims 9-12, 14-15, and 17-18 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement. The rejection is traversed because:

(a) as bacteria are both delivered into the tumor system by cellular carriers and the enzyme is active, the system is efficient for tumor therapy;

(b) the transgenic bacteria expressing a functional prodrug converting enzyme delivered via cells are enriched in the tumor tissue and can functionally convert the

corresponding prodrug in tumor tissue samples and the product of the conversion, 6-Methylpurine (MeP), is known to be toxic to tumor cells, and the combined effect of the enrichment in the tumor tissue and successful conversion is, therefore, directly correlates to the efficacy; and

(c) bacteria loaded cells deliver a recombinant DNA into the tumor tissue which, in turn, is functionally transcribed in the eukaryotic target cells (see claims 31-40 directed to the method of delivering an active protein).

(A) Claims 9-12, 14-15, and 17-18 are directed to a method for prophylaxis or therapy of neoplastic diseases (e.g., claims 9 and 31) and, specifically, cancer (claims 29-30 and 39-40). The Examiner is of the opinion that the present specification and the Declaration of Mr. Fensterle submitted previously is insufficient for the full scope of the claims directed to a method for prophylaxis or therapy. Applicants respectfully disagree.

The data submitted in the Declaration and the Examples of the present specification demonstrate that bacteria loaded cells can deliver a recombinant DNA into the tumor tissue which, in turn, is functionally transcribed in the eukaryotic target cells. As bacteria are both *delivered* into the tumor system by cellular carriers and the enzyme is *active*, the system is efficient for tumor therapy. The experiments also show that tumor of the animal model 4T1 mice is enriched with *Listeria* expressing a functional prodrug-converting enzyme, purine nucleoside phosphorylase (PNP). PNP converts purine pro-drugs to toxic metabolites that <u>are known</u> to cause reduction in tumor growth and prolonged survival. The cells infected with *Listeria* expressing PNP possess a *higher* enzyme activity and, therefore, a *higher* rate of pro-drug to drug conversion compared to controls.

The submitted Declaration presents the experiments conducted with *Listeria* infected 4T1 mice that carry tumors (*in vivo* model).

The question was to demonstrate that transgenic bacteria expressing a functional prodrug converting enzyme delivered via cells are enriched in the tumor tissue and can functionally convert the corresponding prodrug in tumor tissue samples. The product of the conversion, 6-Methylpurine (MeP), is known to be toxic to tumor cells and the combined effect of the enrichment in the tumor tissue and successful conversion is, therefore, directly correlates to the efficacy.

To answer these question, the following method was applied:

a. A recombinant, attenuated *Listeria* strain (*L. monocytogenes* delta aroA) was constructed using standard molecular biology techniques encompassing a plasmid encoding the *E.coli* purimaucleotidephosphorylase (PNP) under the control of the CMV promoter active in eukaryotic cells (DNA delivery). This enzyme mediates the conversion of the prodrug 6-Methylpurine deoxyribose(MePdR) to MeP. The latter product is toxic for tumor cells.

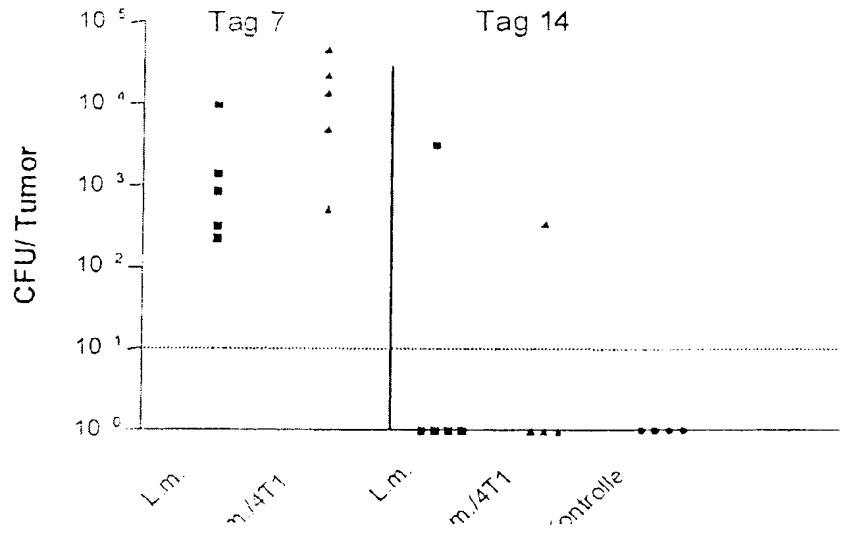
b. Animals were transplanted with 104 4T1 breast cancer cells. Tumors were allowed to grow up to a tumor diameter of approx. 0.5 cm before infection.

c. Animals were infected IV with $1.3x10^6$ recombinant *Listeria* or $2.0x10^7$ bacteria in irradiated 4T1 cells.

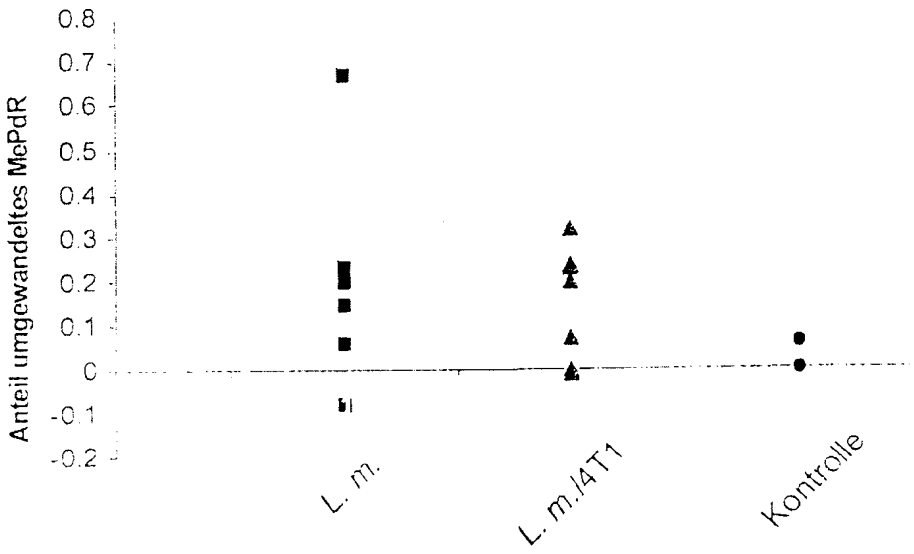
d. The CFU in the tumor tissue was determined by plating serial dilutions 7 days after infection.

e. 7 days after infection, the tumor was excised and homogenized. Tumor lysates were incubated for 48 h with the substrate MePdR. After incubation, the substrate conversion into MeP was assessed by HPLC. The results are expressed as relative amount of formed MeP.

10. The results depicted in the following figure demonstrate that the recombinant *Listeria* strain is effectively delivered into tumor cells in this experimental system (L.m., L.m./4T1, and Control).



The following picture encompasses the enzyme activity 7 days after infection. This picture demonstrates that the bacteria delivered by the irradiated cells can deliver the DNA into the tumor tissue which, in turn, is functionally transcribed in the eukaryotic target cells. As bacteria are both delivered into the tumor system by cellular carriers and the enzyme is active, the system is efficient for tumor therapy.



The experiments show that tumor of the animal model 4T1 mice is enriched with *Listeria* expressing a functional prodrug-converting enzyme, purine nucleoside phosphorylase (PNP). PNP converts purine pro-drugs to toxic metabolites that are known to cause reduction in tumor growth and prolonged survival. The cells infected with *Listeria* expressing PNP possess a higher enzyme activity and, therefore, a higher rate of pro-drug to drug conversion compared to controls. *See* Declaration of Joachim Fensterie with the response filed December 7, 2007.

Thus, the claims are fully enabled for the prophylaxis and/or therapy of neoplastic diseases, e.g., cancer.

(B) In addition, claims 31-40 are directed to a method of *delivering* an active protein. As shown by the data in the Declaration and the Examples 1 and 2 (pages 11-18), bacteria loaded cells deliver a recombinant DNA into the tumor tissue which, in turn, is functionally transcribed in the eukaryotic target cells.

Thus, the claims are fully enabled for delivering an active protein into cells.

Applicants request that the rejection be withdrawn.

Claims 1-4, 6-8, and 19 are rejected under 35 U.S.C. 102(b) over Curtiss et al., US 6,383,496. The rejection is traversed because Curtiss et al. do not describe or suggest that *S. typhimurium* bacteria of Curtiss et al. are capable of prophylaxis or therapy of neoplastic diseases.

The claimed cell is capable of prophylaxis or therapy of neoplastic diseases (cancer), while *S. typhimurium* bacteria of Curtiss et al. are not known to have a therapeutic effect on the cancer cells.

Also, Curtiss et al. study the survival, attachment, and invasion of microphage loaded with the attenuated bacteria, while the claimed isolated mammalian cell is a carrier cell.

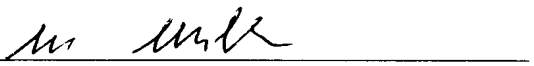
Thus, Curtiss et al. do not anticipate the claimed isolated cell. Applicants request that the rejection be withdrawn.

Claims 20-28 are rejected under 35 U.S.C. 112, second paragraph, as being dependent upon the rejected claims. In view of the submitted amendment and arguments, it is believed that the claims area allowable. Applicants request that the rejection be withdrawn.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Marina I. Miller, Ph.D.
Attorney of Record
Registration No. 59,091

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/07)